Spinal subpial delivery of AAV9 enables widespread gene silencing and blocks motoneuron degeneration in ALS.

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Public Summary:
Gene silencing with virally delivered shRNA represents a promising approach for treatment of inherited neurodegenerative disorders. In the present study we develop a subpial technique, which we show in adult animals successfully delivers adeno-associated virus (AAV) throughout the cervical, thoracic and lumbar spinal cord, as well as brain motor centers. One-time injection at cervical and lumbar levels just before disease onset in mice expressing a familial amyotrophic lateral sclerosis (ALS)-causing mutant SOD1 produces long-term suppression of motoneuron disease, including near-complete preservation of spinal α-motoneurons and muscle innervation. Treatment after disease onset potently blocks progression of disease and further α-motoneuron degeneration. A single subpial AAV9 injection in adult pigs or non-human primates using a newly designed device produces homogeneous delivery throughout the cervical spinal cord white and gray matter and brain motor centers. Thus, spinal subpial delivery in adult animals is highly effective for AAV-mediated gene delivery throughout the spinal cord and supraspinal motor centers.

Scientific Abstract:
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